CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040152

Trade Name : CARISOPRODOL TABLETS USP

Generic Name: Carisoprodol Tablets

Sponsor : ROYCE LABORATORIES, INC.

Approval Date: December 3, 1996

ANDA 40-152

DEC 3

Royce Laboratories, Inc.
Attention: William Stahovec
16600 NW 54 Avenue
Miami, Florida 33014

Dear Sir:

This is in reference to your abbreviated new drug application dated July 10, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Carisoprodol Tablets USP, 350 mg.

Reference is also made to your amendments dated October 21, and November 5, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Carisoprodol Tablets USP, 350 mg to be bioequivalent and, therefore, therapeutically equivalent to that of the listed drug (Soma® Tablets, 350 mg of Wallace Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 12/3/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1. **CHEMIST'S REVIEW NO.:** No.3

2. **ANDA #:** 40-152

3. **NAME AND ADDRESS OF APPLICANT:**
Royce Laboratories, Inc.
Attention: William Stahovec
16600 NW 54 Avenue
Miami, Florida 33014

4. **LEGAL BASIS FOR ANDA SUBMISSION:** See CR #1.

5. **SUPPLEMENTS(s):** N/A

6. **PROPRIETARY NAME:** None used

7. **NONPROPRIETARY NAME:** Carisoprodol Tablets USP, 350 mg

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Royce

07/10/95	ANDA submission (received at OGD on 07/11/95)
02/02/96	Response to NA (MAJOR) letter of 11/20/95
10/21/96*	Response to NA (MINOR) letter of 05/30/96
11/05/96*	Telephone amendment (requested on 11/05/96)

FDA

07/27/95	Acknowledgement letter
11/20/95	NA (MAJOR) letter (from CR #1 by Shing Liu)
05/30/96	NA (MINOR) letter (from CR #2 by Shing Liu)
11/05/96	Requested a telephone amendment

10. **PHARMACOLOGICAL CATEGORY:** Muscle relaxant

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**

13. **DOSAGE FORM:** Tablets

14. **POTENCY:** 350 mg

15. **CHEMICAL NAME AND STRUCTURE:**
See CR #1.

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS**:
It took Royce approximately 5 months to respond to the last NA letter (MINOR AMENDMENT), presumably due to the method validation study which was signed off just three days before they mailed the minor amendment.

There were five chemistry deficiencies in the last NA letter. Afte a preliminary review, the reviewer recommended a telephone amendment to ask Royce to send revised pages of blank batch records. Royce faxed the telephone amendment on the same day of the request. The submitted materials are acceptable.

Labeling, EER (dated 05/13/96), Bioequivalence review are acceptable. DMF of the drug substance was reviewed in connection with this minor amendment, and was found adequate on 11/07/96.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Approvable. An approval package will be prepared.

19. **REVIEWER**:
Shing H. Liu, Ph.D.

DATE COMPLETED:
completed 11/07/96

ANDA 74-152
DUP JACKET
Division File
FIELD COPY

Endorsements:

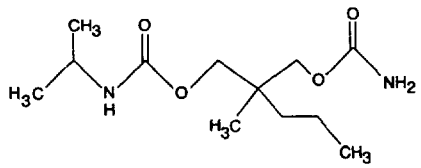
HFD-625/SLiu/11/06/96 Shing Hon Liu 11/07/96
HFD-625/MSmela/
x:\new\firmsnz\royce\ltrs&rev\40152CR3.APP
F/T by 9P/11/12/96

M Smela 11/7/96

CARISOPRODOL TABLETS, USP

DESCRIPTION

Carisoprodol is (±)-2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate. The structural formula is:



Molecular Formula: $C_{12}H_{24}N_2O_4$ Molecular Weight: 260.34

Each round white tablet for oral administration contains 350 mg of carisoprodol. In addition, each tablet contains the following inactive ingredients: Confectioner's sugar, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, and stearic acid.

CLINICAL PHARMACOLOGY

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. The onset of action is rapid and effects last four to six hours.

INDICATIONS AND USAGE

Carisoprodol tablets are indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Carisoprodol is contraindicated in persons with acute intermittent porphyria as well as allergic or idiosyncratic reactions to carisoprodol or related compounds such as meprobamate, mebutamate, or tybamate.

WARNINGS

Idiosyncratic Reactions - On very rare occasions, the first dose of carisoprodol has been followed by idiosyncratic symptoms appearing within minutes or hours. Symptoms reported include: extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Symptoms usually subside over the course of the next several hours. Supportive and symptomatic therapy, including hospitalization, may be necessary.

Usage in Pregnancy and Lactation - Safe usage of this drug in pregnancy or lactation has not been established. Therefore, use of this product in pregnancy, in nursing mothers, or in women of childbearing potential requires that the potential benefits of the drug be weighed against the potential hazards to mother and child. Carisoprodol is present in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. This factor should be taken into account when use of the drug is contemplated in breast-feeding patients.

Usage in Children - Because of limited clinical experience, carisoprodol tablets are not recommended for use in patients under 12 years of age.

Potentially Hazardous Tasks - Patients should be warned that this drug may impair the mental and/or physical abilities required for the performance of the potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Additive Effects - Since the effects of carisoprodol and alcohol or carisoprodol and other CNS depressants or psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.

Drug Dependence - In dogs, no withdrawal symptoms occurred after abrupt cessation of carisoprodol from dosages as high as 1 gm/kg/day. In a study in man, abrupt cessation of 100 mg/kg/day (about five times the recommended daily

adult dosage) was followed in some subjects by mild withdrawal symptoms such as abdominal cramps, insomnia, chilliness, headache, and nausea. Delirium and convulsions did not occur. In clinical use, psychological dependence and abuse have been rare and there have been no reports of significant abstinence signs. Nevertheless the drug should be used with caution in addiction-prone individuals.

PRECAUTIONS

Carisoprodol is metabolized in the liver and excreted by the kidney; to avoid its excess accumulation, caution should be exercised in administration to patients with compromised liver or kidney function.

ADVERSE REACTIONS

Central Nervous System - Drowsiness and other CNS effects may require dosage reduction. Also observed: dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia. (See also Idiosyncratic Reactions under **WARNINGS**.)

Allergic or Idiosyncratic - Allergic or idiosyncratic reactions occasionally develop. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug. Skin rash, erythema multiforme, pruritus, eosinophilia, and fixed drug eruption with cross reaction to meprobamate have been reported with carisoprodol. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock. (See also Idiosyncratic Reactions under **WARNINGS**.)

In case of allergic or idiosyncratic reactions to carisoprodol, discontinue the drug and initiate appropriate symptomatic therapy, which may include epinephrine, antihistamines, and in severe cases corticosteroids. In evaluating possible allergic reactions, also consider allergy to excipients (listed under **DESCRIPTION**).

Cardiovascular - Tachycardia, postural hypotension, and facial flushing.

Gastrointestinal - Nausea, vomiting, hiccup, and epigastric distress.

Hematologic - Leukopenia, in which other drugs or viral infection may have been responsible, and pancytopenia, attributed to phenylbutazone, have been reported. No serious blood dyscrasias have been attributed to carisoprodol.

OVERDOSAGE

Overdosage of carisoprodol has produced stupor, coma, shock, respiratory depression, and, very rarely, death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Any drug remaining in the stomach should be removed and symptomatic therapy given. Should respiration or blood pressure become compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously as indicated. Carisoprodol is metabolized in the liver and excreted by the kidney. Although carisoprodol overdosage experience is limited, the following types of treatment have been used successfully with the related drug meprobamate: diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis (carisoprodol is dialyzable). Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Observe for possible relapse due to incomplete gastric emptying and delayed absorption. Carisoprodol can be measured in biological fluids by gas chromatography (Douglas, J.F. et al: *J Pharm Sci 58*: 145, 1969).

DOSAGE AND ADMINISTRATION

The usual adult dosage of carisoprodol is one 350 mg tablet, three times daily and at bedtime. Usage in patients under age 12 is not recommended.

HOW SUPPLIED

Carisoprodol tablets, 350 mg, are white, round biconvex unscored tablets debossed 376, 350 on one side and the Royce Logo on the other side.

Size	Royce NDC Number
100	51875-0376-1
500	51875-0376-2
1000	51875-0376-4

Storage: Store at controlled room temperature 15-30°C (59-86°F).
Dispense in a tight container as defined in the USP.

Caution - Federal law prohibits dispensing without prescription.

Royce Laboratories, Inc.
16600 N.W. 54 Avenue
Miami, FL 33014

Revised 6/96

NDC 51875-0376-4

Royce™

CARISOPRODOL TABLETS, USP

350 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Each tablet contains:
Carisoprodol, USP ..... 350 mg
Usual Adult Dosage:
One tablet three times daily and at bedtime.
See accompanying information.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Dispense in a tight container as defined in the USP.

EC 3 19

Batch No.:

Exp. Date:

N 3 51875-0376-4 7

NDC 51875-0376-4

Royce™

CARISOPRODOL TABLETS, USP

350 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Each tablet contains:
Carisoprodol, USP ..... 350 mg
Usual Adult Dosage:
One tablet three times daily and at bedtime.
See accompanying information.
Store at controlled room temperature, 15°-30°C (59°-86°F).
Dispense in a tight container as defined in the USP.

3 1996

Batch No.:

Exp. Date:

N 3 51875-0376-4 7

NDC 51875-0376-2

Royce™

CARISOPRODOL TABLETS, USP

350 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

Each tablet contains:
Carisoprodol, USP ..... 350 mg

Usual Adult Dosage:
One tablet three times daily and at bedtime. See accompanying information.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight container as defined in the USP.

Batch No.: 1
Exp. Date:

N 3 51875-0376-2 3

NDC 51875-0376-2

Royce™

CARISOPRODOL TABLETS, USP

350 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. by: Royce Laboratories, Inc., Miami, FL 33014

Each tablet contains:
Carisoprodol, USP ..... 350 mg

Usual Adult Dosage:
One tablet three times daily and at bedtime. See accompanying information.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight container as defined in the USP.

N 3 51875-0376-2 3

Each tablet contains:
Carisoprodol, USP ..... 350 mg

Usual Adult Dosage:
One tablet three times daily and at bedtime. See accompanying information.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight container as defined in the USP.

Royce™

NDC 51875-0376-1

CARISOPRODOL TABLETS, USP

350 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:
Exp. Date:

3 51875-0376-1 6

Each tablet contains:
Carisoprodol, USP ..... 350 mg

Usual Adult Dosage:
One tablet three times daily and at bedtime. See accompanying information.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight container as defined in the USP.

Royce™

NDC 51875-0376-1

CARISOPRODOL TABLETS, USP

350 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:
Exp. Date:

3 51875-0376-1 6

ANDA 40-152

NOV 30 1995

Royce Laboratories Inc.
Attention: Loren Gelber, Ph.D.
16600 NW 54 Avenue
Miami FL 33014

Dear Madam:

Reference is made to your abbreviated new drug application dated July 10, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Carisoprodol Tablets USP, 350 mg.

The following comments pertain **only** to bioequivalency issues in the July 10, 1995 submission.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL 0.05M phosphate buffer pH 6.9 containing 5 units α-amylase at 37°C using USP apparatus 2 at 75 rpm. The test product should meet the following specifications:

   > Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 29 1995

Carisoprodol Tablets, USP
350 mg Tablets
ANDA #40-152
Reviewer: James Chaney
WP# 40152DW.795

Royce Laboratories Inc.
Miami, Florida
Submission Date:
July 10, 1995

Review of Dissolution Data and a Waiver Request

Royce Laboratories has submitted comparative dissolution data on its drug product, Carisoprodol Tablets, USP, 350 mg comparing it to the reference, Wallace's Soma[R], 350 mg tablet, in support of a request waiver of *in vivo* bioequivalence requirements. Carisoprodol produces muscle relaxation and is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. The usual adult dose is one 350 mg tablet, three times daily and bedtime.

Comments:

1. The dissolution method used was correct and satisfactory content uniformity data were submitted for the lot used in the dissolution testing.
2. The comparative dissolution testing data on the test and reference products meet the USP dissolution specifications. The data, method and specifications are shown in Table 1.
3. The test product does not contain any inactive ingredients that may cause a bioequivalence problem. The reference product contains the following inactive ingredients: alginic acid, magnesium stearate, potassium sorbate, starch, and tribasic calcium phosphate. The formulation of the test product is as follows:

Ingredient	Weight/Tablet
Carisoprodol USP	350 mg
Confectioners Sugar NF	
Povidone, USP	
Microcrystalline Cellulose, NF	
Sodium Lauryl Sulfate, NF	
Sodium Starch Glycolate, NF	
Stearic Acid, NF	
Magnesium Stearate, NF	
Total tablet weight	550 mg

4. The reference product, Wallace's Soma[R], 350 mg tablet (carisoprodol tablet, USP, 350 mg) is classified AA in Approved Drug Products with Therapeutic Equivalence Evaluations. Therefore, since the dissolution testing is acceptable there would be no need to conduct an *in vivo* bioequivalence study.

Recommendations:

1. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL 0.05M phosphate buffer pH 6.9 containing 5 units α-amylase at 37C using USP apparatus 2 at 75 rpm. The test product should meet the following specifications:

   Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

2. The dissolution testing conducted by Royce Laboratories on its drug product, carisoprodol tablets, 350 mg, lot #MB-1110, has been found acceptable.

3. The Division of Bioequivalence agrees that the information submitted by Royce Laboratoriess demonstrates that its carisoprodol tablet, 350 mg strength, falls under 21 CFR 320.22 (c) of the Bioavailability/Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to the reference product, Soma^{R} Tablets, 350 mg strength, manufactured by Wallace Laboratories.

The firm should be informed of the recommendations.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

Date 11/29/95

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 11/29/95

cc: ANDA 40-152 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Chaney), Drug File, Division File

JEC/dbm/112995/WP #40152DW.795

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Carisoprodol Tablets, USP
Dose Strength: 350 mg
ANDA No.: 40-152
Firm: Royce Laboratories, Inc.
Submission Date: 07/10/95
File Name: 40152DW.795

I. Conditions for Dissolution Testing:

USP Basket: Paddle: X RPM: 75
No. Units Tested: 12
Medium: 0.05M Phosphate Buffer pH 6.9 containing 5 units α-amylase per mL
Volume: 900 mL
Specifications: NLT . . in 60 min
Reference Drug: Wallace's Soma[R], 350 mg tablet
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MB-1110 Strength (mg) 350			Reference Product Lot # 4I102A Strength (mg) 350		
	Mean %	Range	%CV	Mean %	Range	%CV
15	60.7		11.1	72.8		3.1
30	87.3		2.4	85.6		1.4
45	93.8		1.0	91.2		1.3
60	96.9		1.2	93.8		1.4